I. Flt3 Ligand For Culturing Hematopoietic Cells

For the past ten years, medical scientists have made numerous attempts at using *ex vivo* gene therapy in humans to treat or ameliorate diseases. Until recently, most of the human clinical trials of *ex vivo* gene therapy have yielded equivocal results. However, a group in France reported last month in Science the results of the first *successful* gene therapy treatment (*see* Cavazzana-Calvo *et al.*, 2000, Science:669). Hematopoietic stem cells were taken from the bone marrow of two infant patients suffering from an X-linked form of SCID, and incubated *ex vivo* with a packaged retroviral vector encoding the sequence for a correcting cDNA. After transfusing the transduced stem cells back into the patients, the patients clearly improved by several clinical measurements over several months.

Dr. William French Anderson discusses this exciting development in a commentary in the same issue (*see* Science 288:627-629, [Exhibit A] enclosed). He states that one of *the most significant differences* that distinguished this *successful* human gene therapy trial from earlier attempts is the inclusion of Flt3 ligand[1] in the medium for culturing the hematopoietic cells (see page 628, col. 1, first full paragraph).

The invention, as claimed in the instant application, is directed to hematopoietic cell expansion medias containing Flt3 ligand, and to methods of using Flt3 ligand to expand hematopoietic cells. In various embodiments, Flt3 ligand is combined with other cellular growth factors. As the recent reports in the gene therapy field demonstrate, the use of Flt3 ligand as a culture component is crucial for achieving successful *ex vivo* human gene therapy via hematopoietic cells. Among the large number of cytokines known, Flt3 ligand demonstrates the unexpected activity of stimulating growth of the appropriate early hematopoietic stem cells that is needed for these procedures to effectively work.

II. The Rejections Under 35 U.S.C. §§ 102 And 103 Should Be Withdrawn Because Lyman *et al.* Is Not Prior Art

Claims 1, 2 and 5 are rejected under 35 U.S.C. §102(b) as anticipated by Lyman *et al.* Claims 1 and 2 are directed to hematopoietic cell expansion media containing Flt3-L and methods for expanding hematopoietic cells using the expansion media. Claim 5 is directed to an expansion media that includes Flt3-L and steel factor.

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[1] Although Dr. Anderson's article text states that "Flt3" was used as a growth factor, examination of the original article by Cavazzana-Calvo, particularly footnote 16, makes clear that Dr. Anderson intended to say "Flt3 ligand".

Applicants traverse this rejection. The Examiner concedes that Application No. 08/209,502, filed March 7, 1994, supports priority for the instant claims. The Lyman *et al.* reference was published in December of 1993. This date is less than one year before the filing of the '502 application. Thus, the Lyman *et al.* reference is not available as prior art under 35 U.S.C. § 102(b) and the rejection should be withdrawn.

Further, claims 1 and 2, as amended, and claim 5 are fully supported by the disclosure in the parent Application No. 08/162,407 that was filed on December 3, 1993 *before* the Lyman *et al.* reference was published. For example, page 30, line 4 to page 31, line 33, describes the use of flt3 ligand for hematopoietic cell culture, and flt3 ligand's stimulatory effect on pluripotent hematopeoietic stem cells. It should be noted that claim 5, drawn to hematopoietic cell expansion media containing flt3 ligand and SF (steel factor or c-kit ligand), is also supported by this disclosure because the C-*kit* expressing stem cells were purified using biotinylated Steel factor. Accordingly, Applicants submit that the rejection against these claims must be withdrawn.

Furthermore, the Lyman *et al.* reference is not prior art for any purposes, even under 35 U.S.C. § 102(a). According to 35 U.S.C. § 102(a),

> A person shall be entitled to a patent unless -
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent . . . .

"The real issue is whether *all* the evidence, including the references, truly shows knowledge by another *prior to the time appellants made their invention* or whether it shows the contrary." *In re Land and Rogers*, 151 USPQ 621, 632 (CCPA 1966). As the CCPA noted in *Land*, the significant words in § 102(a) are "known or used by *others* . . . *before* the invention thereof by the applicant." *Id.*, emphasis in original. When all of the evidence of record is considered, including the cited reference by Lyman *et al.*, the basis for the rejection, and Applicants' priority documents, it is clear that Lyman *et al.* is not prior art to the claimed invention.

Lyman *et al.* is cited by the Examiner for the disclosure of a stem cell expansion media comprising cell growth media, flt3 ligand, and steel factor, and a method of expanding hematopoietic cells by contacting the cells with flt3 ligand alone or in combination with steel cell factor. This reference is a publication by the instant inventors and others, which must *necessarily* have happened after the inventors invented the subject matter cited by the Examiner.

Moreover, Applicants parent '407 application, filed December 3, 1993, evidences Applicants' priority for the subject matter cited by the Examiner from Lyman *et al.* "In the case of a reference, it is fundamental that it is valid for what it discloses and if the applicant establishes priority with respect to that disclosure and there is no statutory bar, it is of no effect at all." *In re Stempel*, 113 USPQ 77, 81 (CCPA 1957). In *Stempel*, Applicants established via affidavit that they had a right of priority with respect to subject matter disclosed by a reference. *See also, In re Ziegler*, 146 USPQ 76 (CCPA 1965) (reference disclosing a species of the claimed invention overcome by citation to benefit foreign filed applications that disclosed the same species).

Everything cited by the Examiner in the reference by Lyman *et al.* is contained in the priority '407 application that was filed December 3, 1993—filed *before* the publication of this reference. Accordingly, Applicants have already declared that the subject matter claimed in the '407 application is their invention, and thus have demonstrated priority to their parent U.S. application filed December 3, 1993 for the subject matter referenced by the Examiner in Lyman *et al.*

To summarize, the record makes clear that the subject matter in the cited reference is simply not prior art to the instantly claimed invention. Applicants respectfully submit that the claims are allowable over the cited art.

Claims 1-8 are rejected under 35 U.S.C. §103(a) over the Lyman *et al.* reference, in view of Heimfeld *et al.* and Hoffman *et al.* Since, as demonstrated above, the primary reference, Lyman *et al.*, is not properly cited, this rejection should be withdrawn.

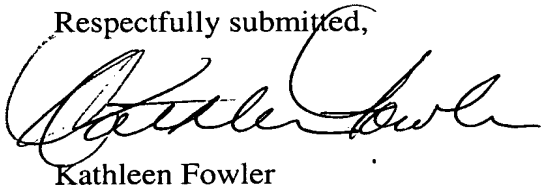
III. Obviousness-Type Double Patenting

Claims 1-8 are provisionally rejected under the doctrine of obviousness-type-double patenting as being unpatentable over claims 1-7, 9 and 10 of copending Application No. 08/399,404. The Examiner asserts that the "conflicting claims are not patentably distinct from each other because the claims of Application No. 08/399,404 are directed to a kit which comprises a cellular growth medium and a growth factor. Since this rejection was a provisional rejection, Applicants request that this rejection be held in abeyance until the claims of the instant application are deemed allowable.

Conclusion

In view of the foregoing remarks, Applicants submit that the claims of the present application are in condition for allowance and respectively request a notice to that effect. If the Examiner believes that any issues outstanding could be resolved by way of a telephone conference, Applicants invite the Examiner to telephone the undersigned at (206)470-4847.

Respectfully submitted,



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